Synopsis – Study 14767B

Title of Study Interventional, open-label, long-term extension study to evaluate the safety and tolerability of brexpiprazole as adjunctive treatment in patients with major depressive disorder
Investigators 18 investigators at 18 sites in 7 countries *Signatory investigator* – [redacted]
Study Sites 18 sites – 2 in Estonia, 1 in Finland, 1 in Germany, 1 in the United Kingdom, 1 in Slovakia, 1 in Sweden, and 11 in the United States
Publications None (as of the date of this report)
Study Period *First patient first visit* – 8 October 2013 *Study terminated* – 1 April 2014 *Last patient last visit* – 13 May 2014
Objectives • *Primary objective*: – to evaluate the long-term safety and tolerability of brexpiprazole (1 to 3 mg/day) as adjunctive treatment to antidepressant (ADT) • *Secondary objectives*: – to evaluate the therapeutic effect of flexible dose (1 to 3 mg/day) brexpiprazole as adjunctive treatment to ADT on: • depressive symptoms • clinical global impression • health-related quality of life – to evaluate the pharmacoeconomics of flexible dose (1 to 3 mg/day) brexpiprazole as adjunctive treatment to ADT
Methodology • This was an interventional, multi-national, multi-centre, open-label, flexible-dose, long-term extension study. • The study included patients who had completed randomised, double-blind lead-in Study 14570A (adults) or Study 14571A (elderly) in major depressive disorder (MDD) with brexpiprazole adjunctive treatment to ADT and who were willing to continue in this extension study. • The study consisted of a Baseline Visit (which was the same as the Completion Visit in the lead-in study), a treatment period where the patients received open-label brexpiprazole treatment adjunctive to ADT (Weeks 0 to 52), and a safety follow-up period (Weeks 52 to 56). • Depending on the patient's age, the dose of brexpiprazole was up-titrated in weekly steps during Weeks 0 to 4 from 1 mg/day (patients aged 18 to 64 years) or 0.5 mg/day (patients aged ≥65 years) to a maximum of 3 mg/day. • During the study (Weeks 4 to 52), the possible doses of brexpiprazole were 1, 2, or 3 mg/day and the dose was preferably to be kept stable in patients with stable symptom severity.

Methodology (continued)

- All patients continued to be treated with commercially available ADT they had received during the lead-in studies (as chosen by the investigator). This was one of the ADTs listed under *Non-investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers*.
- The dose of ADT was the same stable dose the patient received during the lead-in studies and this dose had to remain stable during the initial part of this extension study. Based on clinical judgement, the dose of ADT could be changed from Week 14 onwards within the dose range indicated for the applicable ADT (20 or 40 mg/day for fluoxetine; 20, 30, or 40 mg/day for paroxetine; 60 mg/day for duloxetine; 10 or 20 mg/day for escitalopram [maximum 10 mg/day for patients aged ≥65 years]; 50, 100, 150, or 200 mg/day for sertraline, and 75, 150, or 225 mg/day for venlafaxine).
- Efficacy and safety data were collected at the Baseline Visit, at Weeks 1,2,4, and 8, at 6-week intervals up to Week 44, and at the completion visit (Week 52).
- A safety follow-up visit was scheduled for 4 weeks after completion of the study or after withdrawal from the study.
- This extension study was terminated early because one of the lead-in studies (Study 14571A in elderly) was terminated and because the Sponsor considered that sufficient long-term safety data in the population aged 18 to 65 years had already been collected in the development programme. At study termination, the patients were withdrawn at the next scheduled study visit and treated according to the investigator's judgment.

Number of Patients Planned

1184 patients were planned for enrolment.

Diagnosis and Main Selection Criteria

- Outpatients with a primary diagnosis of MDD according to DSM-IV-TR™ criteria at entry in the lead-in study, who:
  - was judged to benefit from adjunctive treatment with brexpiprazole according to the clinical opinion of the investigator
  - had completed a double-blind, randomised brexpiprazole study immediately prior to enrolment into this extension study

Investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers

Brexpiprazole – 0.5 (titration only), 1, 2, or 3 mg/day; tablets, orally; batch Nos. 2331226 (0.5 mg), 2355962 (0.5 mg), 2331228 (1 mg), 2355963 (1 mg), 2331230 (2 mg), and 2355964 (2 mg), 2331232 (3 mg), and 2355965 (3 mg)

Non-investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers

Duloxetine (*Cymbalta*®) – 60 mg/day; capsules, orally; batch Nos. C222595 (60 mg) and C114103A (60 mg)

Escitalopram (*Cipralex*®) – 5, 10, or 20 mg/day; tablets, orally; batch Nos. 2362697 (5 mg), 2357247 (10 mg), 2361257 (20 mg)

Escitalopram (*Lexapro*®) – 5 or 10 mg/day; tablets, orally; batch Nos. A256954 (5 mg) and A256964 (10 mg)

Fluoxetine (*Prozac*®) – 20 mg/day; capsules, orally; batch Nos. C149697C and 3446A

Paroxetine (*Paxil*® or *Seroxat*®) – 20 or 30 mg/day; tablets, orally; Paxil® batch Nos. 2ZP5499 (20 mg), 3ZP1779 (30 mg); Seroxat® batch Nos. 660M (20 mg) and 057 (30 mg)

Sertraline (*Lustral*™ or *Zoloft*®) – 50 or 100 mg/day; tablets, orally; Lustral™ batch Nos. 37207300U (50 mg), 37206100U (50 mg), 37205404U (100 mg), and 37206300U (100 mg); Zoloft® batch Nos. V130261 (50 mg) and V130513 (100 mg)

Venlafaxine (*Effexor XL*® or *Effexor XR*®) – 75 or 150 mg/day; capsules, orally; Effexor XL® batch Nos. H35772 (75 mg), H14018 (75 mg), and H08096 (150 mg); Effexor XR® batch Nos. V130492 (75 mg) and V130141 (150 mg)

Duration of Treatment

The planned duration of treatment was 52 weeks.

Efficacy Assessments

- Montgomery and Åsberg Depression Rating Scale (MADRS)
- Clinical Global Impression – Severity of Illness (CGI-S)
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-(SF))
- EQ-5D-5L

Pharmacoeconomic Assessments

- Health Economic Assessment (HEA)

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, body mass index (BMI), waist circumference, electrocardiograms (ECGs), electronic Columbia Suicide Severity Rating Scale (eC-SSRS), Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS)

Endpoints

- *Primary endpoints*:
  - description of the safety parameters, see *Safety endpoints* below
- *Secondary endpoints*:
  - depressive symptoms:
    - MADRS total score by visit
    - Proportion of patients in remission (defined as a MADRS total score ≤10) by visit
    - CGI-S score by visit
  - health-related quality of life:
    - Q-LES-Q (SF) total score by visit
    - EQ-5D-5L health state score (VAS) and individual items by visit
  - pharmacoeconomics:
    - resource utilisation during the study using the HEA
- *Safety endpoints*:
  - adverse events
  - absolute values and changes in clinical safety laboratory tests, vital signs, weight, BMI, waist circumference and ECG parameters
  - potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight, and ECG parameter values
  - change in SAS, BARS, and AIMS total scores
  - C-SSRS scores and C-SSRS scores by Columbia Classification Algorithm of Suicide Assessment (C-CASA)

Statistical Methodology

- Only safety analyses were performed. The limited number of enrolled patients resulted in insufficient data for any meaningful efficacy or pharmacoeconomic analyses.
- The following analysis set was used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of Investigational Medicinal Product (IMP) in this study
- Disposition, withdrawals (by primary reason and by all reasons), exposure and compliance (with IMP and ADT), demographics and other baseline characteristics were summarised overall and by lead-in study using descriptive statistics. All patients who withdrew were listed.
- Recent and concomitant medication were classified according to the first dose of IMP (started in the lead-in studies and continued after first dose in this study; and started at or after first dose in this study) and summarised by anatomical therapeutic chemical (ATC) code and generic drug name.

Statistical Methodology (continued)

- Safety assessments were summarised descriptively, overall and by lead-in study, and relative to the baseline of this study.
- The incidences of *treatment-emergent adverse events* (TEAEs) were tabulated by primary system organ class (SOC) and preferred term, by intensity, and by causality (*probably* and *possibly related* to treatment). All adverse events were included in the data listings.
- The number and percentages of patients with suicide-related events, based on the C-SSRS data, were summarised. In addition, the worst case per evaluation of the C-SSRS was mapped into the C-CASA categories (Table 1) and the number and percentage of patients in these categories were summarised.
- The absolute value and change from baseline in SAS total score, BARS Global Clinical Assessment of Akathisia score (Item 4 of the BARS), and AIMS total score were summarised.
- The results of urinalysis were tabulated (dipsticks) and listed (microscopy).
- Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters were summarised descriptively. Post-baseline PCS values were flagged and tabulated. The PCS criterias for clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters are presented in Table 2.
- The total bilirubin level was checked for any patients with increased alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥ three times the upper limits of normal (ULN) or ≥ three times the initial values at baseline. Patients fulfilling the below criteria at any post-baseline visit were listed:
  - ALT or AST ≥3 x ULN OR ≥3 x baseline, AND
  - total bilirubin ≥2 x ULN OR ≥2 x baseline

Sample Size Considerations

No formal sample size calculation was performed for this study. Patients who had completed one of the lead-in studies with brexpiprazole and who fulfilled all the selection criteria for Study 14767B were eligible for this study.

Patient Disposition and Analysis Sets

- Patient disposition overall and by lead-in study is tabulated below:

	Lead-in Study 14570A		Lead-in Study 14571A		Overall	
	n	(%)	n	(%)	n	(%)
Patients enrolled:	3		23		26	
Patients treated:	3		23		26	
Patients completed	0	(0.0)	0	(0.0)	0	(0.0)
Patients withdrawn	3	(100)	23	(100)	26	(100)
Primary reason for withdrawal:						
Adverse event(s)	0	(0.0)	1	(4.3)	1	(3.8)
Lack of efficacy	0	(0.0)	1	(4.3)	1	(3.8)
Non-compliance with IMP	0	(0.0)	1	(4.3)	1	(3.8)
Administrative or other reason(s)	3	(100)	20	(87.0)	23	(88.5)
Analysis set:						
APTS	3		23		26	

Cross-references: Tables 3 and 4
APTS = all-patients-treated set; IMP = investigational medicinal product

- Patient disposition by site is summarised in Table 5.
- Almost all of the patients who entered this extension study had completed lead-in Study 14571A.
- The primary reason for withdrawal during the study was administrative or other reason(s) (Table 4) due to the early termination of the study.
- Withdrawals by all reasons are summarised in Table 6. All withdrawals are in Listing 1.

Exposure

- The overall median exposure to IMP was 59 days (mean: 63 days; Table 7). Compliance with IMP was >80% for all the patients (Table 8). The average mean and modal doses were 1.1 mg/day and 1.2 mg/day, respectively (Table 9). The type of adjunctive ADTs are summarised in Table 10 and the exposure to and compliance with ADT are summarised in Tables 11 and 12, respectively.

Demography and Baseline Characteristics of the Study Population

- The mean age of the 3 patients from lead-in Study 14570A was 44 years (range: 25 to 55 years) and the mean age of the 23 patients from lead-in Study 14571A was 69 years (range: 65 to 78 years). There were 21 women and 5 men and all but one of the patients were White (Table 13). The mean baseline weight, height, BMI, and waist circumference in this study was 79 kg, 166 cm, 29 kg/m^2, and 97 cm, respectively (Table 14).
- The medical history, including concurrent (ongoing at baseline) medical disorders, is presented in Table 15. The medical disorders that were present in >5 patients in this study were *vascular disorders*, *musculoskeletal and connective tissue disorders, gastrointestinal disorders*, *metabolism and nutrition disorders*, and *surgical and medical procedures* (Table 15). This is representative for a population that includes a majority of elderly patients.
- Concomitant medication continued after first dose of IMP and concomitant medication started at or after first dose of IMP are presented in Tables 16 and 17, respectively.
- The physical examination findings at baseline are presented in Table 18.

Efficacy Results

- The limited number of enrolled patients resulted in insufficient data for any meaningful analyses.

Pharmacoeconomic Results

- The limited number of enrolled patients resulted in insufficient data for any meaningful analyses.

Safety Results

Adverse Events

- The adverse event incidence overall and by lead-in study is summarised below:

	Lead-in Study 14570A		Lead-in Study 14571A		Overall	
	n	(%)	n	(%)	n	(%)
Patients treated	3		23		26	
Patients with serious AEs (SAEs)	0		0		0	
Patients with AEs leading to withdrawal	0		1	(4.3)	1	(3.8)
Patients with TEAEs	2	(66.7)	13	(56.5)	15	(57.7)
Total number of TEAEs	2		26		28	

Cross-reference: Table 19
AE = adverse event; SAE = serious adverse event; TEAE = treatment-emergent adverse event

- There were no deaths or other serious adverse events (SAEs) in this study.
- All adverse events are in Listing 2 and all adverse events leading to withdrawal are in Listing 3.
- The TEAEs are summarised by SOC and preferred term in Table 20, by preferred term in Table 21, and by SOC, preferred term, and intensity in Table 22. Related TEAEs are summarised by SOC and preferred term in Table 23.
- Overall, the SOCs with the highest incidence (>10%) of TEAEs were *infections and infestations* (19%), *injury, poisoning and procedural complications* (11.5%), *nervous system disorders* (11.5%), and *psychiatric disorders* (11.5%) (Table 20).
- The TEAEs that were present in ≥2 patients were *accidental overdose*, defined as a dose that exceeded the prescribed dose (3 patients; 11.5%) and *lethargy* (2 patients; 7.7%) (Table 21).

Safety Results (continued)

- One patient withdrew due to an adverse event (*increased glycosylated haemoglobin*; *mild*; *not related*; Listing 3). This patient had not received brexpiprazole, only ADT (sertraline), at the time of onset of the adverse event.
- All the TEAEs were *mild* or *moderate* (Table 22). Eight of the 15 patients with TEAEs had related TEAEs (Table 23).

Extrapyramidal Symptoms Rating Scales (SAS, BARS, and AIMS)

- The SAS total scores and the changes from baseline in SAS total scores are summarised in Tables 24 and 25, respectively. The BARS global clinical assessment of akathisia scores and the changes from baseline in BARS global clinical assessment of akathisia scores are summarised in Tables 26 and 27, respectively. The AIMS total scores and the changes from baseline in AIMS total scores are summarised in Tables 28 and 29, respectively.
- There were no clinically relevant changes in extrapyramidal symptom scores based on the results of the SAS, BARS, and AIMS ratings.

Prolactin Levels and other Clinical Safety Laboratory Parameters

- The clinical safety laboratory values are summarised in Tables 30 (cardiac/skeletal muscle), 31 (electrolytes), 32 (endocrine/metabolic), 33 (haematology), 34 (kidney), 35 (lipids), and 36 (liver). The changes from baseline in clinical safety laboratory values are summarised in Tables 37 (cardiac/skeletal muscle), 38 (electrolytes), 39 (endocrine/metabolic), 40 (haematology), 41 (kidney), 42 (lipids), and 43 (liver). An overview of the reference ranges and the PCS criteria is in Table 2. There were no clinically relevant findings.
- The post-baseline PCS clinical safety laboratory values are summarised in Tables 44 (cardiac/skeletal muscle), 45 (electrolytes), 46 (endocrine/metabolic), 47 (haematology), 48 (kidney), 49 (lipids), and 50 (liver). All PCS clinical safety laboratory values are in Listing 4 and all adverse events in patients with a PCS clinical safety laboratory value are in Listing 5.
- Post-baseline PCS high values were seen for glucose (11 patients; for 8 of them, the value was also PCS high at baseline), urea nitrogen (1 patient), total cholesterol (10 patients; for 4 of them, the value was also PCS high at baseline), low density lipoprotein (LDL) cholesterol (6 patients; for 1 of them, the value was also PCS high at baseline), and triglycerides (6 patients; for 2 of them, the value was also PCS high at baseline). PCS low values were seen for high density lipoprotein (HDL) cholesterol (3 patients; for all of them, the value was also PCS high at baseline).
- One of the patients with post-baseline PCS high glucose (7.5 mmol/L at Week 2) reported *glycosylated haemoglobin increased* as an adverse event at baseline where the glucose value was also PCS high (8 mmol/L); this patient, who did not receive brexpiprazole at the time of onset of the event, was withdrawn from the study due to the event (Listings 3 and 5). There were no adverse events associated with the other PCS high clinical safety laboratory values (Listing 5).
- The urinalysis parameters are summarised in Table 51 and the microscopy results are in Listing 6. The majority of the results were *negative* (ketones, protein, and occult blood) or *normal* (glucose).

ECGs

- The ECG parameter values and the changes from baseline in ECG parameter values are summarised in Tables 52 and 53, respectively. There were no clinical relevant findings.
- The post-baseline PCS ECG values are summarised in Table 54. One patient had post-baseline PCS high QRS duration (132 msec) at Week 8. The value had decreased to 125 msec 14 days later (at study closure) (Listing 7; for an overview of the reference ranges and the PCS criteria, see Table 2). There were no adverse events associated with the PCS high QRS value (Listing 8).

Safety Results (continued)

Vital Signs

- The vital signs and the changes from baseline in vital signs are summarised in Tables 55 and 56, respectively. There were no clinical relevant findings. None of the patients had PCS vital signs (Table 57; for an overview of the reference ranges and the PCS criteria, see Table 2).

Weight and Waist Circumference

- The weight and waist circumference and the changes from baseline in weight and waist circumference are summarised in Tables 58 and 59, respectively. One patient had a PCS weight change (defined as a weight change of ≥7% from baseline) at Week 8 (Table 60 and Listing 9). For an overview of the reference ranges and the PCS criteria, see Table 2. There were no adverse events associated with the weight change (Listing 10).

C-SSRS (C-CASA)

- The baseline and post-baseline C-SSRS scores and C-SSRS scores by C-CASA are summarised in Tables 61 to 64. At baseline, 1 patient had suicidal ideation (*active suicidal ideation with some intent to act, without specific plan*). Post-baseline, none of the patients had suicidal ideation or behaviour (Tables 63 and 64).

Conclusions

- Due to the low number of enrolled patients, no firm conclusions can be drawn regarding the safety beyond short-term treatment; however, the available data indicate that treatment with brexpiprazole (1 to 3 mg/day) adjunctive to a marketed antidepressant was well tolerated in the patients with MDD in this study.
- No conclusions regarding efficacy could be drawn.

Date of the Report

16 February 2015

This study was conducted in compliance with the principles of *Good Clinical Practice*.